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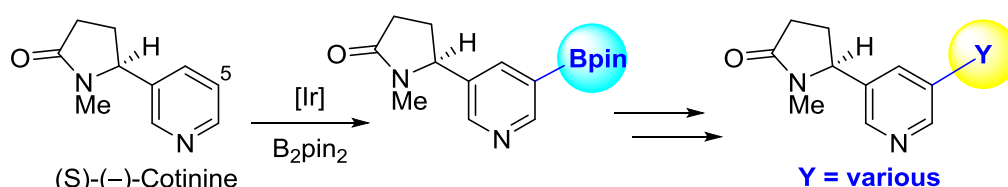
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C(5) Site-Selective Functionalization of (S)-Cotinine

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Abstract

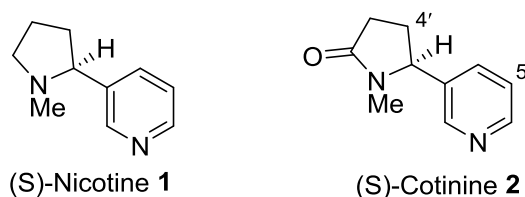
(S)-(-)-Cotinine **2** undergoes direct and site-selective iridium-catalysed borylation to provide boronate ester **3** (and bromide **4**) which offer flexible entry to a range of C(5)-substituted cotinine variants.

Introduction.

The development of small molecule ligands displaying selectivity for key subtypes of nicotinic acetylcholine receptors (nAChRs) has attracted significant interest given the links between nAChRs and neurodegenerative diseases, including Alzheimer's and Parkinson's diseases.¹ Of particular interest is the $\alpha 4\beta 2$ nAChR,² which is the high affinity nicotine subtype present in brain and the therapeutic benefits of a nicotinic-based intervention have been recognised within broader public health issues, such as substance (tobacco and alcohol) addiction.³ Both varenicline (Chantix®)⁴ and cytisine (Tabex®),⁵ which both act as partial agonists for the $\alpha 4\beta 2$ nAChR subtype, are available for smoking cessation. However, alternative approaches to smoking cessation that are also being pursued, and these include vaccine development⁶ (see below) associated with both nicotine and cotinine.

While it is widely accepted that the central nervous system effects of tobacco involve nicotine **1** as the pharmacologically active compound, there is interest in the effects of metabolites resulting from nicotine exposure.⁷ Cotinine **2**, an alkaloid also found in the tobacco plant, has been identified as the major metabolite of nicotine **1** in humans, accounting for 80-85% of

nicotine consumed. Cotinine exhibits a similar pharmacological profile to nicotine **1** (though cotinine is less potent) as well as nAChR activation and desensitization, and also has a much longer plasma half-life (19-24 h) compared to nicotine (2-3 h).⁸ This has led to the suggestion that cotinine **2** may contribute to the physiological effects of tobacco use. Finally, cotinine, which is some 100 times less toxic than nicotine, has not been demonstrated to be addictive or trigger adverse cardiovascular effects.⁹



This distinctive (and comparatively safe) biological profile makes cotinine **2** and variants an attractive class of target, however, there is a lack of efficient and direct synthetic methods for the preparation of cotinine derivatives.¹⁰ Existing synthetic approaches, including gaining access to the heterocyclic core, are either lengthy or rely primarily on oxidation of nicotine derivatives. Previous SAR studies focused on nicotine **1** highlighted the impact of substitution within the pyridyl unit, and Cosford and co-workers¹¹ reported a small library of C(5) functionalised nicotine derivatives which displayed an enhanced subtype selectivity. Svensson and co-workers¹² also targeted the pyridyl C(5), as well as C(6) of nicotine, as the substitution site for hapten generation. Given the profile of cotinine, vaccines based on this metabolite have also been pursued for smoking cessation application, and we^{6f} developed haptens involving modification of C(4') of **2**; this choice was, however, largely dictated by a lack of ready accessibility to the pyridyl ring of **2** at that time. In this paper, we describe an efficient and direct method for accessing C(5) of **2**.

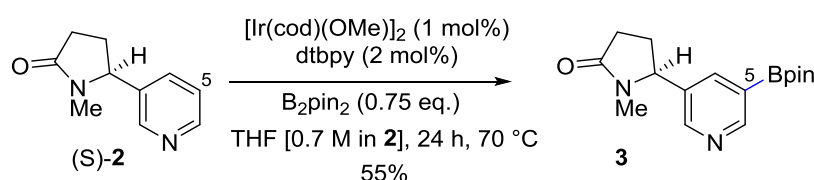
Results and Discussion.

As pyridine modification within cotinine **2** offers a possibility of probing nAChR subtype selectivity, we have sought to achieve direct and specific functionalization of C(5) of **2** and have approached this via C-H activation. Iridium-catalysed borylation has proven to be a highly versatile method of functionalising a range of heterocycles.¹³ With a basic pyridyl nitrogen capable of coordinating to the metal center, pyridyl substrates do, however, present an issue.¹⁴ Certain classes of pyridines do function as efficient substrates for Ir-catalysed

borylation, where the basic center is either sterically shielded or attenuated by electron withdrawing substituents, or both.¹⁵ The use of a bulky “azaphilic” Lewis acid has recently been applied to address regiocontrol in the C-H activation of pyridines.¹⁶

We have assessed the reactivity of cotinine **2** under Ir-catalysed borylation conditions, and these results are summarised in **Scheme 1**. Under standard conditions (using 1 mol% of Ir with Me4phen as ligand) we observed a modest (26%) conversion, but complete regiocontrol with only the desired 5-substituted boronate **3** was observed. However, use of dtbpy, a more basic pyridyl ligand, provided **3** in 55% yield using the same catalyst and ligand loadings. Increasing significantly both catalyst and ligand load to 10 and 20 mol% respectively was assessed but produced only a marginal improvement in yield of **3** (from 55 to 62%). The mass balance in all cases was associated with unreacted **2** but neither addition of further Ir catalyst (after 24 h) nor longer reaction times (to 48 h) improved conversion of **2**. We had previously employed¹⁷ an increased loading of B₂pin₂ in reactions involving secondary or tertiary amines to improve conversion, but in the case of cotinine (with the same catalyst and ligand loading as in **Scheme 1**) this led to a reduction in the isolated yield of **3** and the appearance of small amounts of the 4-borylated adduct (based on ¹H NMR analysis of the crude product).

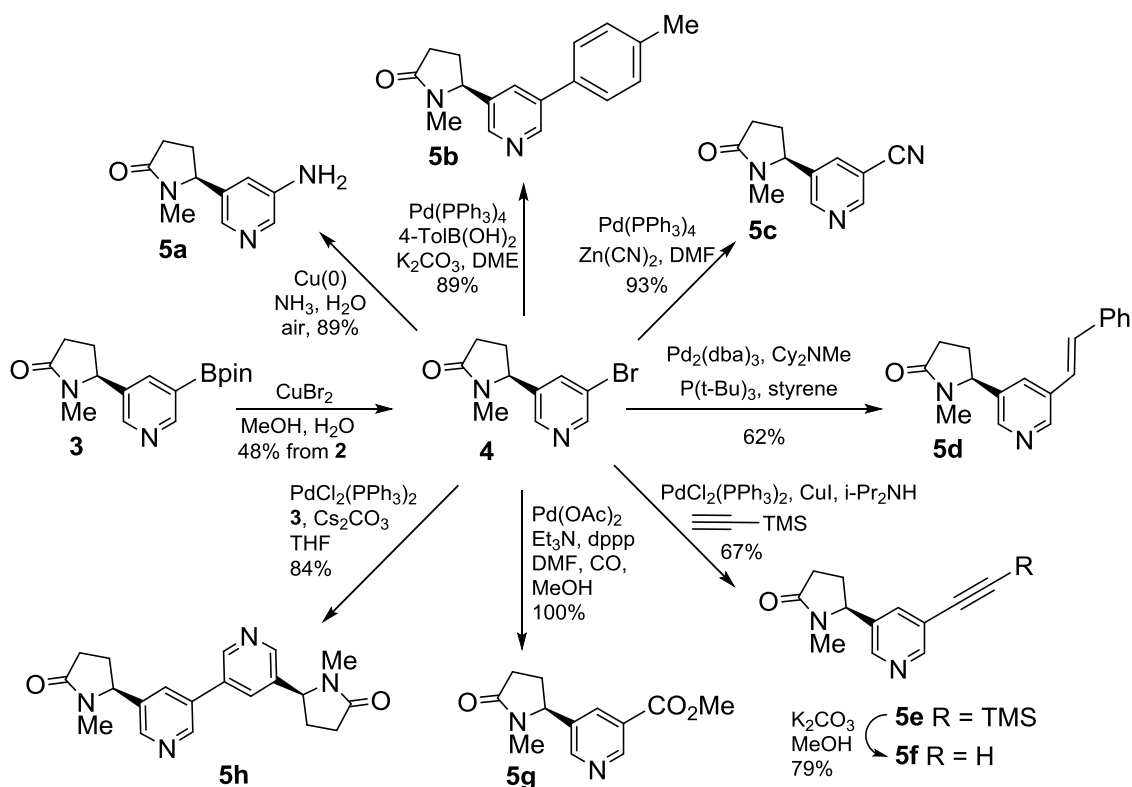
Scheme 1. Ir-catalysed C(5) borylation of (S)-(-)-cotinine 2.



dtbpy = 4,4'-di-tert-butyl-2,2'-dipyridyl; B₂pin₂ = bis(pinacolato)diboron.

In common with a number of pyridyl-based boronates, **3** was prone¹⁸ to protodeboration and though characterised by ¹H NMR, this intermediate was not stable to, for example, chromatography. However, additional purification was unnecessary, and we routinely used “crude” **3** (in a one-pot sequence¹⁹) to generate 5--bromocotinine **4** in 48% overall yield from **2** (Scheme 2). Bromide **4** provides a second ready entry to a library of C(5)-functionalised cotinine derivatives as outlined in **Scheme 2**.

Scheme 2. Reactivity of boronate ester **3** and bromide **4**; access to C(5)-substituted cotinine variants **5a-h**.



Chan-Lam copper-mediated coupling provided the 5-amino variant **5a**, and **4** reacted efficiently under Suzuki-Miyaura, Pd-mediated cyanation, Heck, and Sonogashira cross coupling conditions to give the C(5) aryl as well as alkenyl and alkynyl derivatives **5b-f** respectively. Pd-mediated carbonylation of **4** provided methyl ester **5g** in essentially quantitative yield. The products shown in Scheme 2 offers a representative selection of groupings but this clearly offer a general basis for either direct variation of the component introduced (as in cross coupling cases) or for further functionalisation (via derivatisation of e.g. ester **5g**). Boronate **3** also underwent Suzuki-Miyaura arylation (with an aryl halide partner e.g. BrC₆H₄-4-Me to give **5b**) but our experience was that protodeboration of **3** competed leading to less efficient conversions and more complex product mixtures. However, the novel cotinine-based dimer **5h** is readily generated in 84% yield from direct coupling of **3** with **4**.

Conclusions.

Iridium-catalysed borylation of (–)-cotinine **2** offers direct access to C(5)-substitution within the pyridyl ring and although issues associated with pyridine ligation likely limit overall efficiency, this transformation is nevertheless achieved in reasonable yield. The resulting boronate ester **3** and bromide **4** are then readily manipulated to provide a highly selective entry to C(5) variants of cotinine, which will be assessed in terms of their profiles across a range of nicotinic receptor subtypes.

Experimental.

General Methods.

All reagents were purchased from commercial suppliers and used without further purification unless otherwise stated. Anhydrous solvents were obtained by distillation using standard procedures or by using the Anhydrous Engineering Ltd. with double alumina and alumina-copper catalysed drying columns. NMR spectra were recorded using either a Varian 500 MHz, Varian 400 MHz or JEOL ECP 400 MHz spectrometer, and DEPT135, COSY, HSQC and HMBC were used in assigning NMR spectra. Within ligands **5**, ¹³C NMR signals for C5 and C3 proved difficult to detect in some instances due to signal strength. Mass spectra were determined by the University of Bristol mass spectroscopy service by electrospray ionization (ESI+) using a Bruker Daltonics Apex IV spectrometer equipped with a time-of-flight (TOF) type analyser.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cotinine (3). A Schlenk tube was charged with (–)-cotinine (176 mg, 1.00 mmol), (1,5-cyclooctadiene)(methoxy)iridium (I) dimer (6.6 mg, 0.01 eq.), 4,4'-di-tert-butyl-2,2'-bispyridyl (5.4 mg, 0.02 eq.) and bis(pinacolato)diboron (190 mg, 0.75 eq.). The vessel was placed under vacuum and backfilled with nitrogen three times, dry and deoxygenated THF (1.4 mL) was added and the mixture was heated at reflux for 24 h. The solution was cooled to r.t. and concentrated *in vacuo* without external heating to give crude boronate **3**. ¹H NMR showed a 55% in situ conversion and although boronic ester **3** was unstable to purification by flash column chromatography, this was neither essential nor efficient, and the crude reaction mixture was used in the next step without further

purification. ^1H NMR (400 MHz, CDCl_3) δ = 8.88 (d, J = 1.5 Hz, 1H), 8.52 (d, J = 2.5 Hz, 1H), 7.87 (dd, J = 1.5, 2.5 Hz, 1H), 4.53 (m, 1H), 2.72-2.60 (m, 2H), 1.82-1.70 (m, 2H), 1.34 (s, 3H), 1.25 (s, 12H) ppm.

(-)-5-Bromocotinine (4). 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cotinine (**3**) was made as described above on a 1.0 mmol scale and was used in the next step without any further purification. To an icecold solution of boronic ester **3** in MeOH (2.5 mL) was added an aqueous solution of CuBr_2 (670 mg, 3.0 mmol, 2.5 mL) and the reaction mixture was stirred for 2 days under air. The solution was diluted with NH_4OH (25 mL, 15% aq. sol.) and the aqueous phase was extracted with DCM (3 x 25 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel [DCM/MeOH (1% MeOH)] afforded bromide **4** (120 mg, 48% from **2**) as a paleyellow solid; mp: 93-94 °C (toluene), *lit.*^{10b} 94.5-95.4 °C (methylcyclohexanone/toluene); $[\alpha]_{\text{D}}^{21}$ -16 (c 0.7, MeOH);²⁰ ^1H NMR (500 MHz, CDCl_3) δ = 8.68 (d, J = 2.0 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 7.70 (app t, J = 2.0 Hz, 1H), 4.56 (dd, J = 6.5, 8.0 Hz, 1H), 2.73 (s, 3H), 2.66-2.47 (m, 3H), 1.95-1.87 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ = 175.2, 150.9, 146.4, 138.6, 136.3, 121.4, 61.2, 29.8, 28.4, 28.1 ppm; IR (FTIR) ν_{max} (cm^{-1}): 2975, 1681, 1415, 1380, 1113; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{12}^{79}\text{BrN}_2\text{O}$ 255.0128, Found 255.0121.

(-)-5-Aminocotinine (5a). In a sealed tube, 5-bromocotinine **4** (50 mg, 0.20 mmol) and copper (20 mg, 0.1 eq.) were stirred in aqueous ammonia (0.5 mL, 35% aq. sol.) at 100 °C for 24 h under air. The reaction mixture was cooled to r.t., diluted with ammonia (15 mL, 15% aq. sol.) and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo* yielding **5a** (34 mg, 89%) as colorless solid; mp: 155-157 °C (toluene); $[\alpha]_{\text{D}}^{21}$ -1.1 (c 3.6, MeOH); ^1H NMR (500 MHz, CDCl_3) δ = 8.10 (s, 1H), 7.93 (s, 1H), 6.77 (app t, J = 2.0 Hz, 1H), 4.50 (app t, J = 6.5 Hz, 1H), 3.81 (s, 2H), 2.71 (s, 3H), 2.60-2.45 (m, 3H), 1.93-1.86 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ = 175.6, 143.0, 138.4, 137.5, 137.0, 118.2, 62.0, 30.0, 28.2, 28.0 ppm; IR (FTIR) ν_{max} (cm^{-1}): 3383, 3202, 2922, 1689, 1590; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{10}\text{H}_{14}\text{N}_3\text{O}$ 192.1131, Found 192.1125.

(-)-5-(4-Tolyl)cotinine (5b). A Schlenk tube was charged with 5-bromocotinine **4** (130 mg, 0.5 mmol), potassium carbonate (125 mg, 1.8 eq.), tetrakis(triphenylphosphine) palladium (0)

(28 mg, 5 mol%) and 4-tolylboronic acid (81 mg, 1.2 eq.), placed under vacuum and backfilled with nitrogen three times and 5 mL of a mixture of DME/water (5:1) were added. The reaction mixture was heated at 80 °C for 18 h. The solution was cooled to r.t. and the solvent was removed *in vacuo*. The residue was distributed between water (15 mL) and DCM (15 mL), and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic phases were dried over MgSO₄, filtered and concentrated. Purification of the crude product by flash column chromatography [DCM/MeOH (1.5% MeOH)] afforded **5b** (119 mg, 89%) as a colorless solid; mp: 101-103 °C (toluene); [α]²¹_D -15 (c 2.1, MeOH); ¹H NMR (500 MHz, CDCl₃) δ = 8.83 (d, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 7.67 (app t, *J* = 2.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.65 (app t, *J* = 7.5 Hz, 1H), 2.75 (s, 3H), 2.69-2.50 (m, 3H), 2.44 (s, 3H), 2.00-1.92 (m, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ = 175.4, 148.2, 146.7, 138.5, 137.1, 136.5, 134.2, 131.6, 129.9 (2C), 127.0 (2C), 62.3, 30.0, 28.4, 21.2 (Me) (C5 was not observed) ppm; IR (FTIR) ν_{max} (cm⁻¹): 2968, 2917, 1682, 1393; HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₇H₁₉N₂O 267.1492, Found 267.1490.

(-)-5-Cyanocotinine (5c). In a Schlenk flask were added 5-bromocotinine **4** (55 mg, 0.22 mmol), Pd(PPh₃)₄ (10 mg, 0.04 eq) and zinc cyanide (30 mg, 1.2 eq) and the flask was placed under vacuum and backfilled with nitrogen for three times. Dry DMF (1.0 mL) was added, and the reaction mixture was heated at 90 °C for 24 h. The solution was cooled to r.t. and the solvent was removed *in vacuo*. Purification by flash column chromatography [DCM/MeOH (1% to 3% MeOH)] afforded **5c** (40 mg, 93%) as a colorless solid; mp: 119-122 °C (toluene); [α]²²_D -22 (c 2.5, MeOH); ¹H NMR (500 MHz, CDCl₃) δ = 8.87 (d, *J* = 2.0 Hz, 1H), 8.70 (d, *J* = 2.0 Hz, 1H), 7.80 (t, *J* = 2.0 Hz, 1H), 4.62 (m, 1H), 2.72 (s, 3H), 2.65-2.47 (m, 3H), 1.91-1.82 (m, 1H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ = 175.2, 152.1, 151.6, 137.5, 136.9, 116.0, 110.6, 61.6, 29.6, 28.5, 28.2 ppm; IR (FTIR) ν_{max} (cm⁻¹): 2927, 2231, 1711, 1681, 1567, 1453, 1384, 1271; HRMS (ESI) *m/z*: [M+H]⁺ Calcd for C₁₁H₁₂N₃O: 202.0975, found: 202.0978.

(-)-5-((E)-2-Phenylethenyl)cotinine (5d). To a mixture of 5-bromocotinine **4** (130 mg, 0.50 mmol) and Pd₂(dba)₃ (5.7 mg, 2.5 mol%) in dry dioxane (2.5 mL) was added Cy₂NMe (0.1 mL, 1.1 eq.), P(*t*-Bu)₃ (0.1 M in dioxane, 0.25 mL, 5 mol%) and styrene (60 μ L, 2.0 eq.). The mixture was stirred at r.t. for 24 h under a nitrogen atmosphere. After 24 h, Pd₂(dba)₃ (5.7 mg, 2.5 mol%), P(*t*-Bu)₃ (0.1M in dioxane, 0.25 mL, 5 mol%) and styrene (60 μ L, 2.0 eq.) were

added again and the reaction was stirred for a further 24 h more. The solution was filtered through a short pad of Celite®, washed with EtOAc and concentrated *in vacuo*. The crude reaction mixture was purified by flash column chromatography on silica gel [DCM/MeOH (1% MeOH)] to give styrene **5d** (85 mg, 62%) as a pale yellow oil; $[\alpha]^{21}_{\text{D}} -14$ (c 5.8, MeOH); ^1H NMR (500 MHz, CDCl_3) δ = 8.72 (d, J = 2.0 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 7.65 (app t, J = 2.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 17.0 Hz, 1H), 7.10 (d, J = 17.0 Hz, 1H), 4.62 (m, 1H), 2.75 (s, 3H), 2.71-2.50 (m, 3H), 2.00-1.91 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ = 175.5, 148.4, 147.1, 136.6, 136.3, 133.5, 131.7, 130.6, 128.8 (2C), 128.5, 126.7 (2C), 124.1, 62.2, 30.0, 28.4, 28.3 ppm; IR (FTIR) ν_{max} (cm^{-1}): 3437, 3024, 2971, 1678, 1392; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}$ 279.1492, Found 279.1488.

(-)-5-(2-Trimethylsilylethynyl)cotinine (5e). To a mixture of 5-bromocotinine **4** (95 mg, 0.38 mmol), CuI (7 mg, 10 mol%) and $\text{PdCl}_2(\text{PPh}_3)_2$ (13 mg, 5 mol%) in dry THF (10.0 mL) was added *i*-Pr₂NH (0.15 mL, 3.0 eq.) followed by trimethylsilylacetylene (0.1 mL, 1.1 eq.) and the mixture was stirred at r.t. for 36 h under a nitrogen atmosphere. The solution was diluted with DCM (50 mL) and the organic layer was washed with NH_4Cl (10 mL, 15% aq. sol.), brine (10 mL), dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel [DCM/MeOH (1.5% MeOH)] afforded **5e** (67 mg, 67%) as a colorless solid; mp : 96-98 °C (toluene); $[\alpha]^{21}_{\text{D}} -66$ (c 0.3, MeOH); ^1H NMR (500 MHz, CDCl_3) δ = 8.73 (br s, 1H), 8.47 (br s, 1H), 7.60 (s, 1H), 4.57 (app t, J = 6.5 Hz, 1H), 2.71 (s, 3H), 2.68-2.46 (m, 3H), 1.96-1.86 (m, 1H), 0.30 (s, 9H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ = 175.4, 152.3, 147.1, 136.4, 100.8, 99.5, 61.9, 29.8, 28.3, 28.1, -0.26 (3C) ppm, (C3 and C5 have not been detected); IR (FTIR) ν_{max} (cm^{-1}): 2155, 1683, 1392; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{21}\text{N}_2\text{OSi}$ 273.1417, Found 273.1420; $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{15}\text{H}_{20}\text{N}_2\text{NaOSi}$ 295.1237, Found 295.1243.

(-)-5-Ethynylcotinine (5f). To a solution of 5-(2-trimethylsilylethynyl)cotinine **5e** (60 mg, 0.22 mmol) in a mixture of MeOH/DCM (2:1) (6 mL) was added K_2CO_3 (60 mg, 2 eq.) and the reaction mixture was stirred for 24 h under a nitrogen atmosphere. Water (10 mL) was added and the aqueous phase was extracted with DCM (3 x 15 mL). The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo*. Purification of the crude reaction mixture by flash column chromatography [DCM/MeOH (1% MeOH)] afforded **5f** (35 mg, 79%)

as a colorless oil; $[\alpha]^{21}_D$ -11 (c 1.5, MeOH); ^1H NMR (500 MHz, CDCl_3) δ = 8.71 (s, 1H), 8.48 (s, 1H), 7.63 (s, 1H), 4.57 (m, 1H), 2.71 (s, 3H), 2.65-2.46 (m, 3H), 1.93-1.86 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ = 175.6, 152.3, 147.7, 136.7, 81.5, 79.7, 61.8, 29.8, 28.4, 28.1 (C3 and C5 have not been detected); IR (FTIR) ν_{max} (cm^{-1}): 3202, 2928, 2852, 1681, 1381; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}$ 201.1022, Found 201.1015.

(+)-Methyl cotinine-5-carboxylate (5g). A solution of 5-bromocotinine **4** (45 mg, 0.18 mmol), Et_3N (0.1 mL, 2.5 eq.), dppp (15 mg, 0.2 eq.) and $\text{Pd}(\text{OAc})_2$ (8 mg, 0.2 eq.) in DMF/MeOH (1:1) (0.9 mL) was stirred at 80 °C under CO (1 atmosphere, balloon) for 24 h. The mixture was cooled to r.t., filtered through Celite® and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel [DCM/MeOH (1.5% MeOH)] afforded **5g** (43 mg, quantitative) as a colorless solid; mp: 93-94 °C (toluene); $[\alpha]^{21}_D$ +40 (c 0.1, MeOH); ^1H NMR (500 MHz, CDCl_3) δ = 9.22 (s, 1H), 8.70 (s, 1H), 8.15 (s, 1H), 4.65 (app t, 1H, J = 7.5 Hz), 4.00 (s, 3H), 2.71 (s, 3H), 2.68-2.50 (m, 3H), 1.95-1.88 (m, 1H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ = 175.4, 165.3, 152.0, 150.8, 136.7, 134.8, 126.6, 61.9, 52.6, 29.8, 28.4, 28.3 ppm; IR (FTIR) ν_{max} (cm^{-1}): 1654, 1549, 1457; HRMS (ESI) m/z : $[\text{M}+\text{Na}]^+$ Calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{NaO}_3$ 257.0897, Found 257.0898.

(+)-5-(Cotinin-5-yl)cotinine (5h). 5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)cotinine (**3**) was prepared on a 0.50 mmol scale as described above and was used in the next step without further purification. Over the crude reaction mixture of **3**, 5-bromocotinine **4** (73 mg, 0.28 mmol), caesium carbonate (233 mg, 0.72 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (10 mg, 5 mol%) and THF (3 mL, 0.1 M) were added, and the reaction mixture was stirred at reflux for 48 h. The solution was cooled to r.t., water (15 mL) was added and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organic phase was dried over MgSO_4 , filtered and concentrated. Purification of the residue by flash column chromatography [DCM/MeOH (4% MeOH)] yielded **5h** (59 mg, 84%) as a colorless solid; mp: > 200 °C; $[\alpha]^{21}_D$ +18 (c 0.5, MeOH); ^1H NMR (500 MHz, CDCl_3) δ = 8.84 (s, 2H), 8.59 (d, J = 2.0 Hz, 2H), 7.69 (app t, J = 2.0 Hz, 2H), 4.69 (app t, J = 7.5 Hz, 2H), 2.76 (s, 6H), 2.71-2.51 (m, 6H), 2.03-1.93 (m, 2H) ppm; ^{13}C NMR (125 MHz, CDCl_3) δ = 175.5, 148.2, 148.1, 137.2, 133.4, 132.2, 62.2, 30.0, 28.5, 28.4 ppm; IR (FTIR) ν_{max} (cm^{-1}): 3043, 2925, 1681; HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_4\text{O}_2$ 351.1816, Found 351.1812.

Associated Content.

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^1H and ^{13}C NMR spectra for compounds **4** and **5a-h**, and ^1H NMR spectra of crude borylation reaction mixture comprising cotinine **2** and boronate ester **3**.

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The authors declare no competing financial interest.

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